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Review Article

Case-Control Trials on Risk Factors for Pancreatic Cancer: A Systematic Review and Meta-Analysis

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Abstract

Background: The single risk factors of pancreatic cancer (PC) has been extensively studied. We aimed to synthesize results from such studies to identify and estimate multiple independent risk factors of PC.

Methods: Articles published up to Feb 28, 2020 in English or Chinese reporting risk factors of PC were reviewed. The fixed-effects model with 95% confidence interval (CI) were used to calculate the pooled Odds Ratio (OR). Data were analyzed using RevMan 5.3.

Results: PC was significantly associated with smoking (*OR*: 1.76, 95% *CI*: 1.61–1.92, $P < 0.00001$, $I^2 = 6\%$), diabetes (*OR*: 2.69, 95% *CI*: 2.52-2.88, $P < 0.00001$, $I^2 = 0\%$), family history of PC (*OR*: 2.58, 95% *CI*: 2.13-3.11, $P < 0.00001$, $I^2 = 0\%$), and chronic pancreatitis (*OR*: 5.84, 95% *CI*: 3.63-9.41, $P < 0.00001$, $I^2 = 0\%$).

Conclusion: Smoking, diabetes, family history of PC, and chronic pancreatitis were independent risk factors for PC. These independent risk factors have an important role in identifying high-risk groups, which is of great significance to reduce the incidence of PC and improve the quality of life and prognosis of patients.

Keywords: Pancreatic cancer; Risk factor; Systemic review; Meta-analysis; Case-control trials

Introduction

Pancreatic cancer (PC) is a high-grade gastrointestinal malignancy that ranks fourth in cancer-related deaths in the United States, with a 5-year survival rate of no more than 9% (1). It is noteworthy that pancreatic cancer is the only cancer with increasing mortality rates, and is expected to become the second most common cause of cancer-related death by 2030 (2). PC could be treated early (3). With a definite diagnosis, the 5-year survival rate can be increased to 46% (4).

The main diagnostic approaches of PC are clinical manifestations, imaging screening methods, serum tumor markers, and molecular biology gene diagnosis. While the use of a single marker or imaging detection at a specificity and sensitivity may not be significant or accurate, multiple

detection might be more reliable. In practice, most of the integrated technologies for screening are able to improve greatly the overall diagnosis rate of PC, but the large population of China determine that the use of multiple detection will result in very high screening costs and low detection efficiency. Therefore, we need to identify new breakthroughs in the context of technological bottlenecks and economic restrictions.

Increasingly, studies have focused on crowd differentiation in cancer screening, such as lung cancer to narrow precisely the range of high-risk groups. Smoking has been identified as the only independent risk factor for PC (4,5). Due to the controversial findings of a previous study based on smaller sample size, we systematically assessed risk factors of PC associated with smoking, diabetes, chronic pancreatitis, and family history of PC by meta-analysis.

Methods

Eligibility criteria for articles

Identified articles were grouped into the following categories: (i) articles related to PC risk factors; (ii) articles of case-control studies in which the case group was patients with confirmed PC, while the control group was composed of subjects not related to PC, and there were more than 100 samples in both the case group and the control group;(iii) articles with accurate original data; and (iv) articles in which the full text can be accessed in a public database.

The following articles were excluded: (i) articles not related to PC risk factors; (ii) articles with a sample size of less than 100 for either the case group or the control group; (iii) articles repeatedly publishing the same sample data; (iv) articles that were not available in full text; and (v) summaries, letters, abstracts, brief exchanges, and case reports.

Literature search method

The Web of Science, PubMed, Embase, Medline, Cochrane Library, Chinese National Knowledge Infrastructure (CNKI), and the Wan Fang database were searched using the MESH Terms 'Pancreatic Cancer', 'Risk Factor' and 'Case-Control Study'. Articles related to PC risk factors were initially screened using the phrases 'pancreatic cancer' and 'risk factor'. Case-control studies were retrieved from the preliminary screening results. The retrieval period was up to February 28, 2018. The languages of the articles were limited to Chinese and English. Data was summarized from the eligible articles and a meta-analysis was performed to explore the association between risk factors and PC.

Statistical analysis

A database was established using Microsoft Excel (Version 15.23). The data types were determined and appropriate effect indicators were selected. The meta-analysis was performed using the Inverse Variance method according to the Cochrane system by RevMan5.3. OR and 95% CI were used to evaluate the relationship between PC and risk factors such as smoking, diabetes, chronic pancreatitis, and family history of PC. Heterogeneity was tested by forest plot, Q test, and I^2. $P>0.1$ or $I^2<50$ % indicated that there was no heterogeneity or low heterogeneity in the effect quantity between studies, and the fixed-effect model was adopted. Instead, the random effects model was selected. Potential publication bias was assessed by analysis of funnel plots. If the graph presented a symmetrical inverted funnel shape, there was no publication bias; otherwise, publication bias existed.

In this study, two authors (KJX and YY) independently reviewed the selected articles and extracted the following data: first author, year of publication, sample area, study time, source of case and control samples, sample number of case group and control group, and analysis method. All the analyses were resolved by discussion. The quality of inclusion criteria was assessed using the Newcastle-Ottawa scale (NOS). This study selected articles with a score of 6 or above.

Results

According to the inclusion criteria, 655 publications were obtained through the initial search. The selection process for eligible papers included

in this meta-analysis is presented in Fig. 1. Thus, the final meta-analysis included 22 publications, 24,181 cases, and 38,554 controls. The detailed characteristics of individual study are listed in Table 1. In these studies, samples were collected from 1990 to 2016, and the geographical distribution of the examined samples included seven countries (China, the United States, Italy, Canada, the Netherlands, Poland, and Australia). The NOS scores ranged from 6 to 8 stars, indicating that all the included studies were of high quality. Smoking was the only identified risk factor. Individual studies had different conclusions for each risk factor. In this study, 22 case-control studies with a reference rate more than 15% and the first four risk factors (mentioned by more than 3 articles) with higher consensus were selected for detailed analysis of their combined *OR* in Table 2.

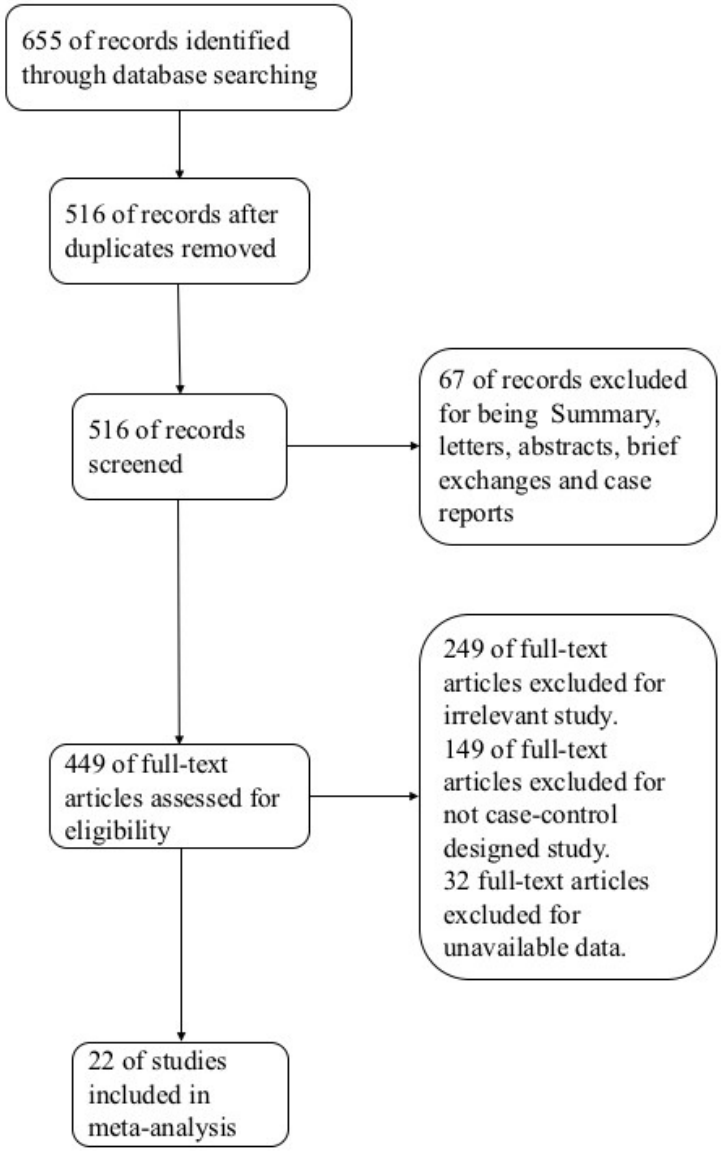

Fig. 1: Flow chart of study selection

Table 1: Information of the 22 articles enrolled in the meta-analysis

Study	*Country*	*Start - stop time of research*	*Sample sources*		*Sample size*		*NOS score*
			Case	**Control**	**Case**	**Control**	
Zhang XH,2006 (6)	China	1990-1993	A new case of pancreatic cancer has been reported in Shanghai	A population matched by sex and age	451	1552	6
Qiu DY,2004 (7)	China	1995-2001	Elderly pancreatic cancer patients admitted to zhongshan hospital affiliated to fudan university	The elderly hospitalized patients with the same gender and age were randomly selected	167	167	7
Zhou GZ,2002 (8)	China	1993-2001	Second military medical university confirmed case of pancreatic cancer patients	The date of hospitalization, date of birth, nationality, gender and frequency of residence of the same hospital without tumor or endocrine disease	493	1031	8
Chen M,2014 (9)	China	2011-2013	Patients with pancreatic cancer in henan cancer hospital	The family members of the non-pancreatic cancer patients in the same disease area or other disease areas shall be required to be the same sex as the patients, have an age difference less than 5 years, and live in henan province	105	105	8
Yan D,2010 (10)	China	2002-2007	Patients with pancreatic cancer in the first affiliated hospital of xinjiang medical university	Concomitant nontumor inpatients	207	210	7
Zhou GZ,2002 (11)	China	1993-2001	Changhai hospital, Oriental liver and gallbladder hospital and long march hospital were diagnosed as inpatients with pancreatic cancer	The date of hospitalization, date of birth, nationality, gender and residence frequency of patients admitted to the hospital without tumor or endocrine diseases match	1031	1239	8
Xu P,2011 (12)	China	2000-2010	Pancreatic cancer patients admitted to the provincial hospital affiliated to anhui medical university	Patients with concurrent nontumor and nonmetabolic diseases with the lowest inpatient number 3 were randomly selected	290	312	8
Zhao JQ,2018 (13)	China	2005-2016	PC patients admitted to cangzhou people's hospital	Patients with non-tumor and non-metabolic diseases were hospitalized at the same time	580	624	7
Yao Y,2013 (14)	China	2006-2013	Peking union medical college hospital and other 4 hospitals han pancreatic cancer patients	A han Chinese health checker from Peking union medical college hospital who was matched in the same period	180	360	7
Peng LN,2014 (15)	China	2011-2013	The first affiliated hospital of zhengzhou university met the diagnostic criteria for pancreatic	Concomitant hospitalization physical examination normal population	147	164	6

			cancer inpatients				
Chen Q,2012 (16)	China	2002-2012	Pancreatic cancer patients hospitalized in east China	In the same period, patients were hospitalized for multiple reasons and acute diseases, and their gender and age matched	916	1124	6
Yang MW,2017 (17)	China	2010-2016	Pancreatic cancer patients admitted to the first affiliated hospital of the third military medical university	Healthy persons who underwent physical examination in our hospital at the same time	246	246	5
Silverman DT,1999 (18)	Canada	1986-1989	The population cancer registries of Atlanta, Detroit, and New Jersey recorded cancer patients aged 30 to 79 years	The general population in the study area was selected and matched with the expected age, race and gender distribution of the control group. The control group aged 30-64 was selected by random number dialing	484	2099	7
Zheng Z,2016 (19)	China	2011-2013	Patients with pancreatic cancer have been diagnosed in four hospitals, namely henan cancer hospital, Beijing cancer hospital, hebei cancer hospital and Beijing academy of medical sciences cancer research hospital	Family members of other hospitalized patients without pancreatic cancer at the same hospital	323	323	8
Anderson LN,2009 (20)	Canada	2003-2007	Pancreatic cancer patients registered in Ontario from 2003 to 2007	A random sample of Ontario residents	422	312	7
Bosetti C,2014 (21)	In Italy	2014	PANC4 alliances, 15 case control studies	PANC4 alliances, 15 case control studies	8305	13987	7
Ben Q,2011 (22)	China	2000-2009	Patients diagnosed with pancreatic cancer at Shanghai ruijin hospital and changhai hospital	Patients admitted at the same time for any acute condition	1458	1528	7
Talamini R,2009 (23)	In Italy	1991-2008	Pancreatic cancer patients diagnosed at major general hospitals in northern Italy	Patients with acute non-tumor diseases admitted to the same hospital	326	652	7
Maisonneuve P,2010 (24)	Canada, Netherlands, Poland, Australia	1983-1988	Cases of pancreatic cancer were provided by hospitals in Toronto, Canada; Utrecht, the Netherlands; Opole individual hospital and cancer registry in Poland; south Australia cancer registry in Adelaide, Australia; and 19 developmental hospitals in Montreal, Canada	Other cases of patients at the same centre	823	1679	8
Pang T,2017 (25)	China	1997-2013	Patients diagnosed with PDAC at the medical	Residents of the same area as the case group	1274	3630	8

			center of the affiliated hospital of zhejiang university school of medicine				
Hassan MM,2008 (26)	USA	2001-2006	Pancreatic cancer patients diagnosed and treated at the gastroenterology oncology clinic at the university of Texas Anderson cancer center	Non-healthy friends and genetically unrelated family members (spouses and in-laws) of pancreatic, gastrointestinal, lung or head and neck cancers (smoking-related cancers)	808	808	7
Rahman F,2015 (27)	Canada	2011-2012	Pancreatic cancer patients recruited by the pancreatic cancer institute of Ontario	Population-based frequency matching with pancreatic cancer cases (1:3)	345	1285	8

Table 2: Reference rates of risk factors in the 22 enrolled articles (reference number >3; reference rate≥15%)

Risk factors	*Reference number (N)*	*Reference rate (%)*
Smoking	12	54.55
Diabetes	8	36.36
Family history of pancreatic cancer	8	36.36
Chronic pancreatitis	4	18.18

Relationship between smoking and PC

Smoking is the only confirmed independent risk factor for PC. Previous studies (9,10,12,13-16,19,20,22,23,26) generally held a unified view on this conclusion, but the correlation results of different individual studies were disparate. In this study, *OR* was combined from 12 studies that cited smoking as a factor. The results of a heterogeneity analysis are shown in Fig. 2 (A), while publication bias is detailed in Fig. 3. There was low heterogeneity among the results of independent studies, so the fixed-effect model was selected. Moreover, there was a significant association between smoking and PC occurrence. The combined results were statistically significant, but there was publication bias (*OR*:1.76, 95% *CI*: 1.61–1.92, $P < 0.00001$, $I^2 = 6\%$).

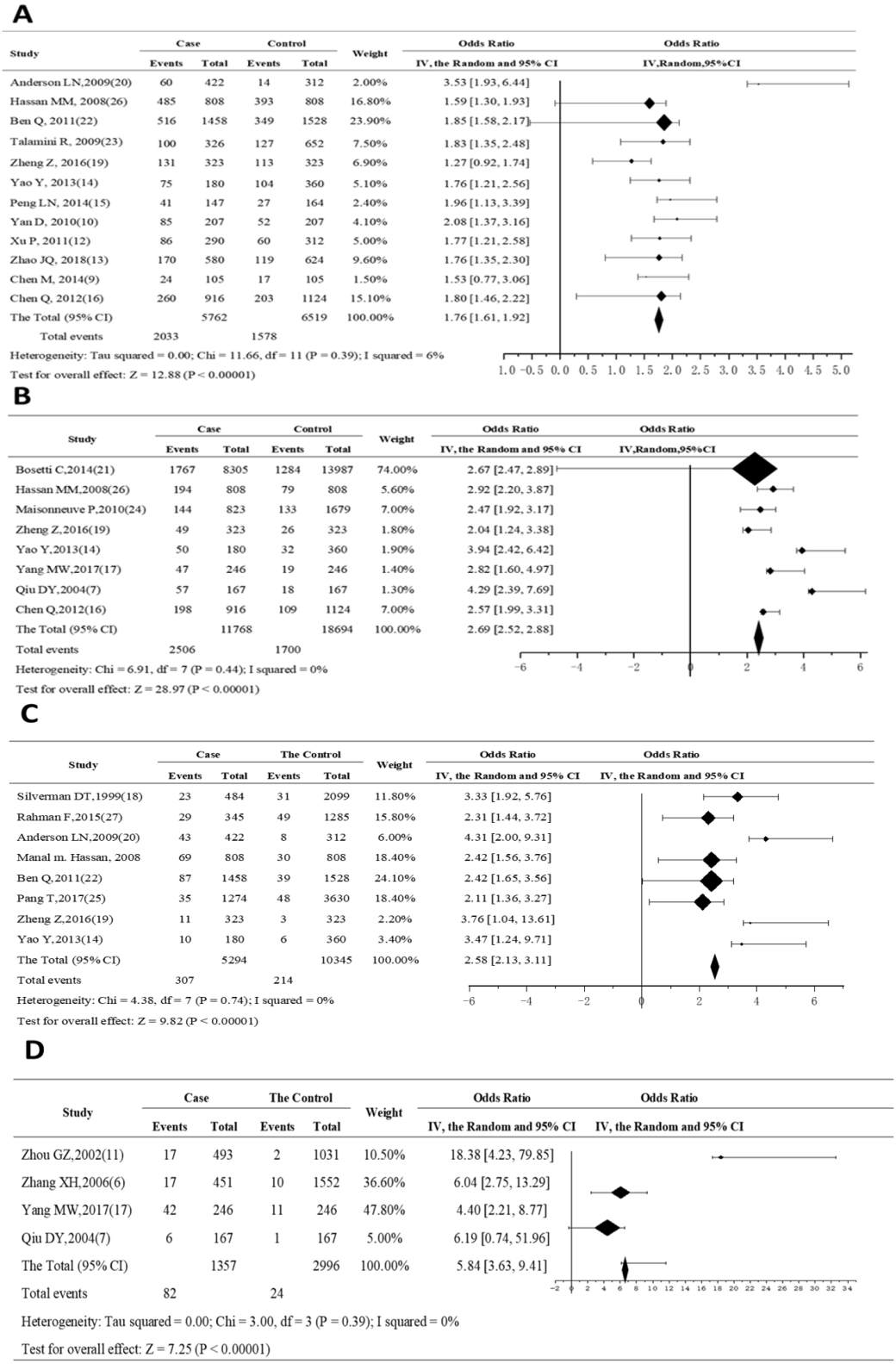

Fig. 2: Results of a meta-analysis on the risk of pancreatic cancer associated with smoking (A), diabetes (B), family history of PC (C) and chronic pancreatitis (D)

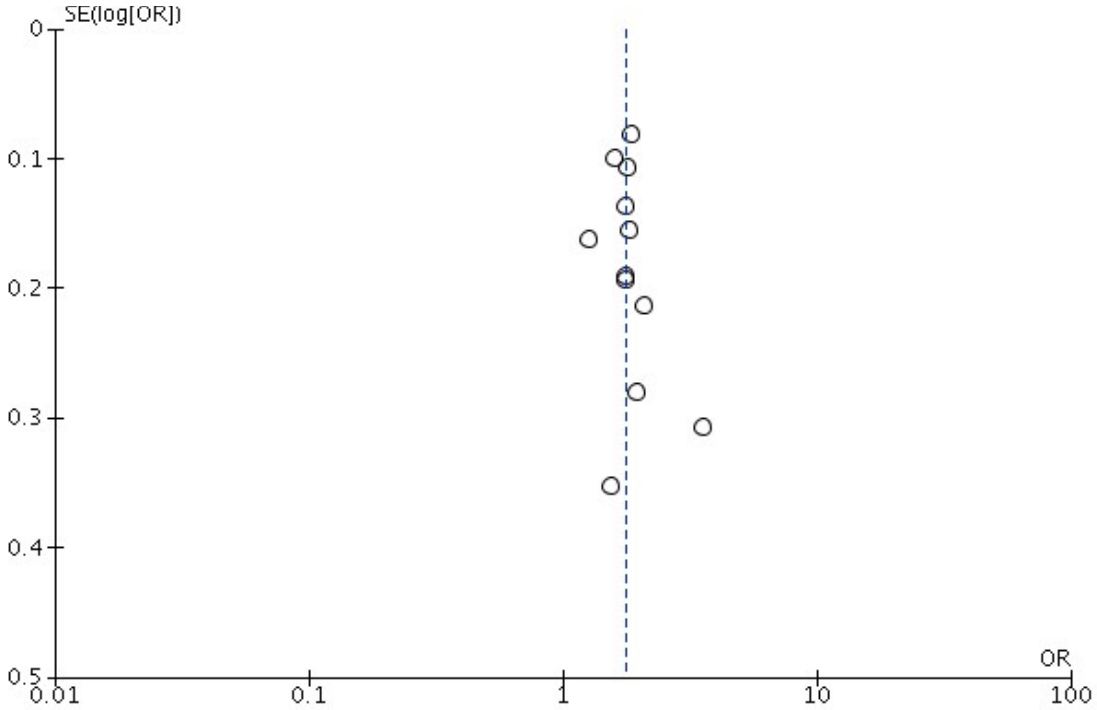

Fig. 3: Publication bias of literature describing the association between smoking and PC tested by funnel plot

Relationship between diabetes and PC

In recent years, studies on the risk of diabetes for PC have gradually increased, and increasing numbers of studies have confirmed diabetes as a risk factor of PC. In this study, OR was combined from 8 studies (7,14,16,17,19,21,24,26) that mentioned diabetes as a factor. Fig. 2 (B) demonstrates the analysis result of heterogeneity, and because the number of included studies was <10, we did not assess the publication bias. There was no heterogeneity among the results of independent studies, so the fixed-effect model was selected. There was a significant association between diabetes and PC (*OR*: 2.69, 95% *CI*: 2.52–2.88, $P < 0.00001$, $I^2 = 0\%$).

Relationship between family history of PC and PC

Using the data of 8 articles (14,18,19,20,22,25,26,27) included in this study that mentioned family history of PC, OR was combined and calculated, and heterogeneity was analyzed (Fig. 2 (C)). Because the number of included studies was <10, we did not assess the publication bias. There was no heterogeneity among the results of independent studies, so the fixed-effect model was selected. Furthermore, there was a significant association between family history of PC and PC (*OR*: 2.58, 95% *CI*: 2.13–3.11, $P < 0.00001$, $I^2 = 0\%$).

Relationship between chronic pancreatitis and PC

The risk of PC for pancreatitis, chronic pancreatitis, and acute pancreatitis has not yet been determined. This study selected chronic pancreatitis with the highest consensus for the meta-analysis. Using the data of 4 articles (6,7,11,17) included in this study that mentioned chronic pancreatitis, *OR* were combined and calculated and heterogeneity was assessed (Fig. 2 (D)). Because the number of included studies was <10, we did not assess the publication bias. There was no heterogeneity among the results of independent studies, so the fixed-effect model was selected. There was a significant association between chronic pancreatitis and PC (*OR*: 5.84, 95% *CI*: 3.63–9.41, $P < 0.00001$, $I^2 = 0\%$).

Discussion

Smoking is recognized as an independent risk factor for PC. Becker et al. demonstrated that smoking is a high-risk factor of PC or one of its early manifestations (28). Smoking increases the risk of PC (29). At the same time, the risk of PC was clearly apparent among young smokers and heavy smokers (30). Current studies suggest that carcinogens in tobacco are transmitted through the respiratory tract and then through the blood flow to the pancreas, and are ultimately absorbed. Nitrosamines-4- (methyl nitrosamines) in tobacco flow into the pancreas through the pancreatic duct. 1-(3-Pyridine)-1-butanone has an important role in the development of PC (31,32). Our results showed that smoking was an independent risk factor for PC (OR = 1.76, P < 0.05). Therefore, smoking cessation is an important measure to reduce the incidence of PC.

Diabetes mellitus is closely related to the occurrence of PC (30, 31). People with high levels of fasting and postprandial blood sugar have a 2.49 times higher risk of pancreatic cancer than those with low levels (31). Glucose disorders, especially postprandial hyperglycemia, might pass through mitochondrial electron transport chains to result in excessive production of superoxide products, which is also the cascade reaction that leads to diabetes (33). Furthermore, peroxide concentrations of hydrogenase and glutathione peroxidase in the pancreatic tissue of PC patients were found to be lower (34). These results suggest that oxidative stress can regulate PC activity. Diabetes mellitus is closely related to PC; chronic hyperglycemia causes abnormal metabolism and activation of related pathways, ultimately promoting the occurrence of PC. The same was true in this study. We identified diabetes mellitus as a risk factor for PC (OR = 2.69, P < 0.05). Thus, it is important to take corresponding measures to prevent diabetes mellitus and reduce the incidence of PC.

Approximately 4%–16% of PC incidence is related to genetic factors (35). In PC relatives, the risk of *BRCA2* mutation was significantly higher in cousins of patients with PC than those of the control group (35). This study showed that family history of PC was a risk factor for PC (OR = 2.58, P < 0.05). Therefore, people with a family history of PC should be more vigilant to PC; regular physical examinations should be performed and serum CA199 levels should be checked if necessary. Endoscopic ultrasound and CT combined screening with ERCP is an effective method for the early diagnosis of PC.

The results of this study showed that chronic pancreatitis was an independent risk factor for PC (OR = 5.84, P < 0.05). In an important genetic cohort study, Lowenfels et al. found that PC occurs more often in patients with chronic pancreatitis (36). Although a few studies argued that this relationship is controversial, many case-control studies and cohort studies have found chronic pancreatitis is a risk factor for PC. In particular, patients with rare autosomal hereditary pancreatitis exhibit more intense symptoms. In these patients, the link between pancreatitis and pancreatic cancer was 70 times stronger than in the general population, and lifelong risk is approximately 40%–55%.

According to our analysis, there was publication bias in smoking, which might be due to the limited number of reports included. Therefore, further studies are needed to verify the conclusions. However, there is no heterogeneity that can be used to prove the reliability of our conclusions.

Conclusion

Smoking, diabetes, family history of PC, and chronic pancreatitis are independent risk factors for PC. These findings of independent risk factors might have an important contribution in identifying high-risk groups and preventing the occurrence of PC. It is of great importance to reduce the incidence of PC to improve the quality of life and prognosis of patients.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Conflict of interests

The authors have declared that they have no competing interests.

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